## *REMARKS*

### *Status of the Claims*

Claims 20-36 are pending in this application. Claims 1-19 have been canceled. Claims 20-36 have been added. No new matter has been added by the above new claims. The newly submitted claims are more specific than the earlier presented claims in terms of the essential ingredients present in the preparation. For reasons that will be discussed below, it is submitted that the prior art does not suggest the invention defined by the current claims. Applicants reserve the right to file a continuation application containing additional claims at a future date.

### *Interview Summary*

Applicants acknowledge with appreciation the personal interview held with Supervisory Examiner Venkat on October 5, 2004 and the subsequent telephone interview held with Examiner Kishore on October 13, 2004. The Interview Summary faxed on October 19, 2004 summarizes the main points of discussion during the interview held on October 13, 2004. During the telephone interview conducted on October 13, the Applicants' representative proposed claim

amendments to distinguish from the disclosure of Iida '317. The Examiner commented on the proposed amendments and made further suggestions. Some of the matters discussed during the above interviews will be further summarized and explained in the following remarks.

***The Present Invention***

The present invention is directed to a preparation that can be used to deliver a material to the large intestine part of the lower gastrointestinal tract of a subject. As the Examiner is aware, the conditions in the large intestine are unique. In this regard, there is a certain pH range in the large intestine, as well as a certain temperature in the large intestine and there are certain bacterial flora and enzymes present in the large intestine, etc. However, the actual conditions in the large intestine can vary between patients and, in fact, can vary from time to time in a particular patient depending upon the health of the patient and foods the patient has recently eaten.

One of the important features of the present invention is that it can deliver a material specifically to the large intestine. The present invention accomplishes release of the

material to be delivered to the large intestine in a completely different manner than the prior art. Although the pH in the lower intestine is usually lower than the pH in the upper intestine, it is considered that the pH in the cecum is uncontrollable in humans as described in Watanabe et al. USP 6,368,629 at col. 3, lines 25-40. The desirable property of the present invention (site specific delivery) is not easily affected by variation of physiological conditions in the large intestine. For example, if the pH fluctuates due to the influence of sickness or diet, the preparation of this invention can still be disintegrated at the specific site. The release of a material to be specifically delivered in the large intestine is site specific, but not dependent upon pH. Many factors may affect the disintegration of the disintegration layer in accordance with the present invention in the large intestine. It is believed that one of the factors is the reducing condition, which breaks down the disulfide bonds in the cystine molecule. This may be one factor that contributes directly or indirectly to disintegration of the disintegration layer.

***Rejections Under 35 U.S.C. § 112***

Claims 1, 3-11, 13 and 15-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants appreciate the Examiner's careful review of the claims and his clear explanation of the basis for the rejection. Reconsideration and withdrawal of this rejection are respectfully requested in light of the new claims and the following remarks.

With respect to the enteric coating, this coating is indicated as being a required component in new claim 20, and all claims dependent thereon. However, it is respectfully submitted that it is not necessary to claim the presence of an enteric coating in order to overcome the prior art rejections. Additionally, the present application discloses products that are not enterically coated. For example, when the preparation of claim 20 is in the form of a capsule, an empty capsule is first prepared. This empty capsule can be sold as a commercial product for use in delivery of a variety of different substances. Such empty capsules would typically be filled with a substance to be delivered, such as a drug, and then later coated with an enteric coating. For instance,

new claim 27 and some of the claims dependent thereon such as claim 30, encompass such empty or uncoated capsules.

With respect to previous claims 10 and 19, these claims have been cancelled. It is submitted that the language used in the new claims is clear and does not raise the issues presented in previous claims 10 and 19.

For the above reasons, it is submitted that the newly presented claims are not confusing or indefinite and fully comply with 35 USC 112, second paragraph.

***Rejections Under 35 U.S.C. § 102***

Claims 1, 3-4, 8-11, 13-17 and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Iida (U.S. Patent 5,057,317). The Examiner has referred in particular to Example 4 at cols. 7 and 8 of Iida '317. Applicants thank the Examiner for specifically identifying the relevant parts of the cited reference. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are respectfully requested.

While Applicants do not concede the propriety of the rejection, in a spirit of cooperation and in order to advance the prosecution of the present application, the new claims have been drafted to

indicate that the preparation comprises a matrix comprising chitosan and particles of cystine dispersed in the matrix. Iida does not suggest the specific combination of these two ingredients as recited in the new claims. For example, the cystine containing layer in Example 4 (the outer layer) contains hydroxyproplylmethyl cellulose, not chitosan. Additionally, as will be discussed further below with respect to the obviousness rejection, chitosan is not equivalent to hydroxypropylmethyl cellulose. As such, Applicants respectfully request the withdrawal of the anticipation rejection.

***Rejections Under 35 U.S.C. § 103***

Claims 1, 3-11, 13 and 15-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Iida '317 in combination with Lo (U.S. 5,516,530) by itself or in combination with Watanabe (U.S. 6,368,629) of record.

Iida is directed to slow-release pharmaceutical preparations. The preparation contains a pharmaceutical agent, a binder such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose or corn starch (see, Col. 4, lines 22-41 and the Examples) and a "slow-release rendering additive". The layer containing the

pharmaceutical agent also contains the binder and the slow-release rendering additive.

The Examiner has cited Lo for teaching the equivalency of hydroxypropylmethyl cellulose or chitosan, and pectin (see page 5, second paragraph of the Office Action). The Examiner has cited Watanabe for its teachings concerning chitosan. In this regard, the Examiner has stated that Watanabe "teaches that chitosan in colon specific drug delivery tablets reacts with enterobacteria in the lower part of the gastrointestinal system with the subsequent delivery of the active agent (abstract)" (see page 5, third paragraph of the Office Action).

The above rejection is respectfully traversed for the following reasons.

**Iida is not properly combinable with Watanabe**

The Examiner has relied on Watanabe for it's teaching that chitosan is susceptible to enterobacteria in the lower part of the GI tract with subsequent delivery of the active agent. There is no indication in Watanabe that there is a problem with utilizing the chitosan containing compositions that would need to be solved. Since there is no problem that needs to be solved, it would not be obvious to modify the compositions of Watanabe. Pursuant to *In re*

*Sernaker*, 217 USPQ 1, 6 (Fed. Cir. 1982), the prior art references must suggest an advantage to be gained from combining the references. No such suggestion is present in the cited references.

Contrary to the suggestions of the prior art, the attached Declaration teaches that chitosan alone does not selectively disintegrate in the large intestine (see the casting film consisting of chitosan results in the Table in the Declaration). In light of this result, there would be no reason for one of ordinary skill in the art to turn to Iida for its teachings concerning cystine, particularly since the composition of Watanabe appears to work perfectly well for the invention of Watanabe. For the foregoing reasons, it is respectfully submitted that a prima facie case of obviousness has not been established based on the combination of Watanabe and Iida.

**Chitosan is not equivalent to ethylcellulose (EC) and hydroxypropylmethyl cellulose (HPMC)**

The Examiner has relied on Lo for its teaching of the equivalency of HPMC and chitosan. Attached hereto is a Declaration by Yumio Kudo, one of the inventors of the present invention. This Declaration establishes that chitosan is not equivalent to HPMC.

**The present invention produces important unexpected results**

As discussed above, an important objective of the present invention is the ability to selectively deliver a substance to the large intestine. In order to accomplish this, it is desirable for the matrix of the disintegration layer to be resistant to disintegrating in the small intestine. The matrix of the disintegration layer should however disintegrate in the large intestine. The results of the Declaration are summarized in the Table on page 8 of the Declaration. The Table shows that of the four different films tested, only the chitosan + cystine film was resistant to disintegration in BCB (a test solution that simulates the environment in the small intestine) and disintegrates in C-BCB (a test solution that simulates the environment in the large intestine). This Declaration shows the unexpected and improved results achieved by the specific combination of materials recited in the claims.

**The technology to which the present invention pertains is unpredictable.**

The attached Declaration, in addition to showing that HPMC is not equivalent to chitosan, also establishes that EC is not equivalent to chitosan. Thus, the evidence of record collectively

establishes that there is a high level of unpredictability in the technology to which the present invention pertains, particularly with respect to the properties of different matrix materials. Evidence of unpredictability in the technology is evidence of non-obviousness, pursuant to *In re May*, 197 USPQ 601, 611 (CCPA 1978).

For the foregoing reasons, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness and even if it is determined that a prima facie case of obviousness has been established, Applicants submit that the present invention is patentable as evidenced by a showing of nonobviousness provided in the attached Declaration.

***Conclusion***

It is respectfully submitted that the present application is in condition for allowance. Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Gerald M. Murphy, Jr. (Reg. No. 28,977) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a response in connection with the present application. The required fee of $450.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Attachments: Declaration Under 35 U.S.C. § 1.132
with attached reference of Tozaki et al.